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FLUORESCENCE QUENCHING INDUCED BY SEQUENTIAL ADDITION–AROMATIZATION OF A BODIPY-CONTAINING DIENYLIMINE WITH THIOLS

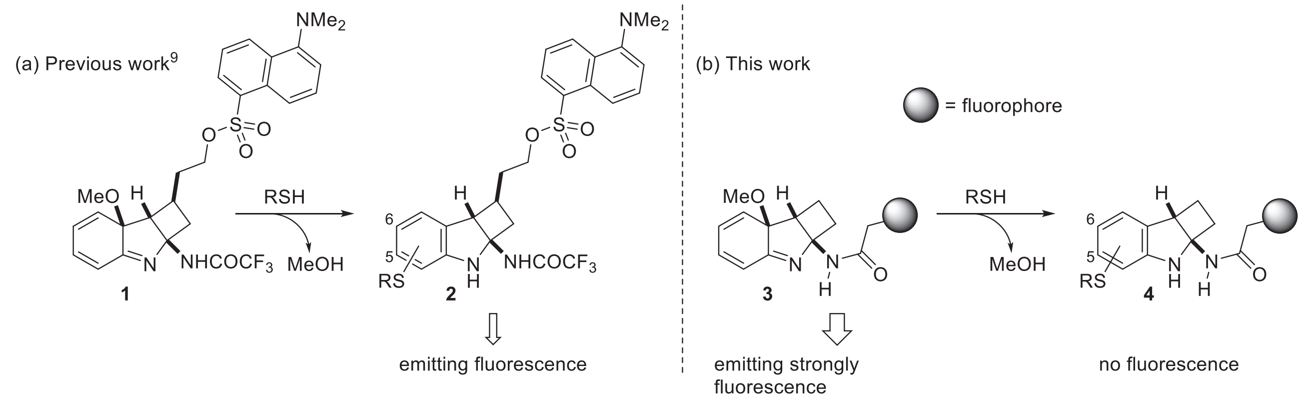
Norihiko Takeda, Masafumi Ueda, Nagisa Mori, Tetsuya Miyoshi, Manami Shimoda, Yumina Uno, Hiroshi Kitagawa, Noriaki Emoto, Takahiro Mukai, and Okiko Miyata*

Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan; E-mail: miyata@kobepharma-u.ac.jp

Abstract – Treatment of a dienylimine bearing a boron–dipyrromethene (BODIPY) fluorophore with aryl and alkyl thiols afforded arylthio and alkylthio–indolines through an addition–aromatization reaction sequence. The structural change from the dienylimine moiety to the indoline–nucleus is important process in this fluorescence quenching.

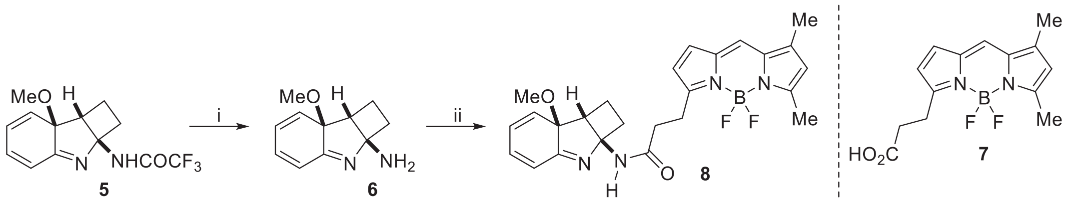
The development of thiol-selective labeling reagents that recognize biothiols such as cysteine, homocysteine, and glutathione has attracted considerable attention in the field of bioorganic chemistry because biothiols play an important role in maintaining biological redox homeostatis.[1] As a result, a number of organic reactions have been used to design various fluorescent thiol probes.[2] These include cyclization reactions between aldehydes and aminothiols,[3] Michael addition reactions,[4] cleavage reactions of 2,4-dinitrobenzenesulfonyl group with thiols,[5] nucleophilic substitution reactions,[6] disulfide exchange reactions,[7] and others.[8] We recently reported thiol-selective labeling reagent **1**, which is based on a novel type of addition–aromatization reaction [Scheme 1 (a)].[9] Sequential reaction of **1** with thiophenol and octanethiol afforded corresponding indoline **2**, which contains an aromatic carbon–sulfur bond achieved through a Michael-type 1,4-addition followed by aromatization with concomitant elimination of MeOH. Furthermore, the fluorescence intensity of dienylimine **1**, which bears a dansyl fluorophore, increased over the course of the reaction. In this work, we have further studied the thio Michael addition–aromatization sequence using dienylimine **3**, which has a boron-dipyrromethene (BODIPY) group as the fluorophore, and found that sequential reaction of fluorescent **3** with thiophenol (R = Ph) induced drastic fluorescence quenching [Scheme 1 (b)].

The BODIPY dyes have been applied extensively in chemo- and biosensors and bioimaging because they strongly absorb in the UV-vis region and have high fluorescent quantum yields, sharp fluorescence emissions, high photophysical stability, and low sensitivity to the polarity and pH of their environment. Although “turn-off” fluorescent sensors utilizing a variety of fluorophores have been developed,[10] little is known about the fluorescence quenching of thiol-selective labeling reagents bearing a BODIPY fluorophore. We herein report that the sequential reaction of BODIPY-bearing dienylimine **3** with a variety of thiols gave arylthio and alkylthio–indolines **4**, which showed drastic fluorescence quenching [Scheme 1 (b)].



Scheme 1. Thiol-selective labeling reagent based on Michael addition–aromatization of dienylimines **1** and **3** bearing leaving group with thiols. The fluorophore is BODIPY in (b).

We initially examined the preparation of dienylimine **8**, which bears a BODIPY fluorophore at the amino group. Dienylimine **8** was prepared by removal of the trifluoroacetyl group of dienylimine **5**[9] with aqueous ammonia, followed by condensation of amino–dienylimine **6** with BODIPY-containing carboxylic acid **7**[11] (Scheme 2).

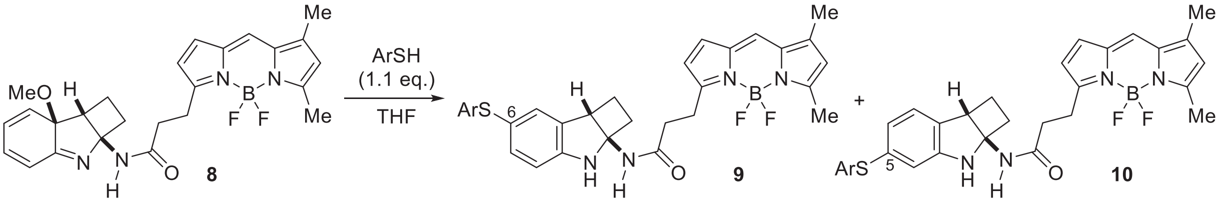


Scheme 2. Preparation of dienylimine **8** bearing a BODIPY fluorophore. Reagents and conditions: i, aqueous NH_3 (28%), MeOH, reflux, 3.5 h, ii, **7**, EDCI, HOBt, *i*Pr_2NEt, CH_2Cl_2, rt, 18 h, 93% (2 steps).

With dienylimine **8** in hand, we proceeded to investigate addition–aromatization reactions with thiophenol (Table 1). We have previously reported that addition–aromatization reactions of dienylimine with thiophenol proceed at ambient temperature to afford 6- and 5-phenylthioindolines in moderate yields.[9] Therefore, we first performed the reaction of **8** with thiophenol (1.1 eq.) at ambient temperature.

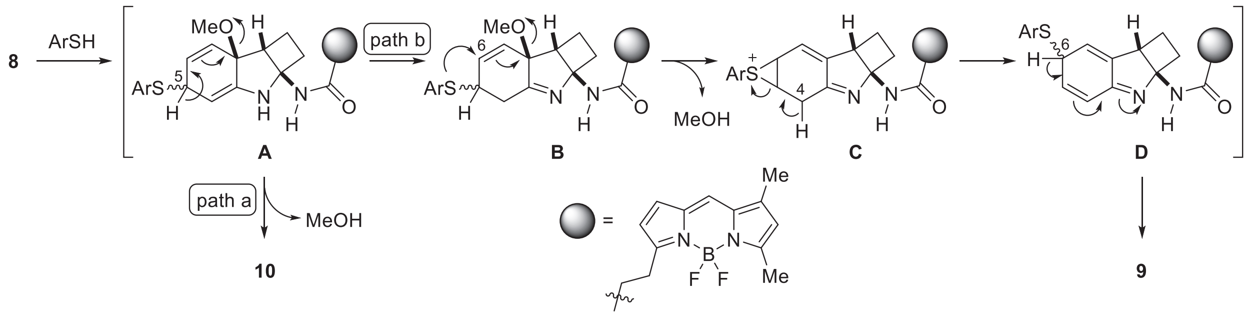
As expected, addition–aromatization reactions of **8** proceeded to give 6- and 5-phenylthioindolines **9a** and **10a** in 68% and 9% yields, respectively (entry 1). However, sequential reaction was inefficient because of the long reaction time (5 days) required for complete conversion of **8** into indolines **9a** and **10a**. Pleasingly, when the reaction was performed at 40 °C, the sequential reaction was completed within 12 h to give indolines **9a** and **10a** in a combined yield of 82% (entry 2). Addition–aromatization reactions of **8** with *p*-fluorophenylthiol afforded indolines **9b** and **10b** in 64% and 15% yields, respectively (entry 3), whereas the use of *p*-methoxyphenylthiol led to a slightly increased combined yield of **9c** and **10c** (86%, entry 4). The regioisomeric ratios were 4:1–9:1 in favor of 6-arylthioindolines **9a**–**c** (entries 1–4). To confirm the high selectivity of the dienylimine moiety for thiols, we next examined the sequential reaction of **8** with various arylthiols bearing amino and hydroxyl groups at the *p*-, *m*-, and *o*-positions. These reactions proceeded smoothly to give 6-arylthioindolines **9d**–**9i** in good to high yields without the formation of 5-arylthioindolines **10d**–**i** (entries 5–10).[11]

Table 1. Addition–aromatization reactions of dienylimine **8** with various aryl thiols



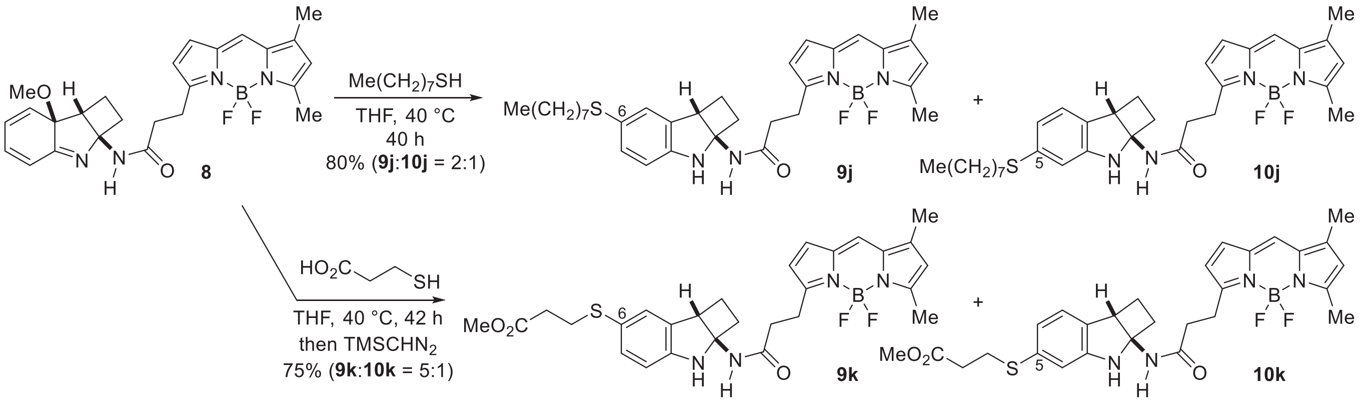
Entry	ArSH	Temp	Time	Yield (**9**)	Yield (**10**)
1	PhSH	rt	5 days	**9a**: 68%	**10a**: 9%
2	PhSH	40 °C	12 h	**9a**: 68%	**10a**: 14%
3	*p*-FC_6H_4SH	40 °C	33 h	**9b**: 64%	**10b**: 15%
4	*p*-$MeOC_6H_4SH$	40 °C	21 h	**9c**: 78%	**10c**: 8%
5	*p*-$H_2NC_6H_4SH$	40 °C	9 h	**9d**: 99%	**10d**: ND
6	*p*-HOC_6H_4SH	40 °C	24 h	**9e**: 96%	**10e**: ND
7	*m*-$H_2NC_6H_4SH$	40 °C	22 h	**9f**: 82%	**10f**: ND
8	*m*-HOC_6H_4SH	40 °C	16 h	**9g**: 92%	**10g**: ND
9	*o*-$H_2NC_6H_4SH$	40 °C	12 h	**9h**: 75%	**10h**: ND
10	*o*-HOC_6H_4SH	40 °C	13 h	**9i**: 86%	**10i**: ND

Based on our current results as well as previous results,[9] we have proposed a possible reaction pathway for the formation of 6-arylthioindoline **9** and 5-arylthioindoline **10** (Scheme 3). The addition of arylthiol would have occurred preferentially at the 5-position of dienylimine **8** to generate enamine **A** in the reaction system. The aromatization reaction of **A** with concomitant an elimination of methanol (path a) leads to the formation of 5-arylthioindoline **10**, in which **10** would be obtained via the deprotonation at the 5-position. In contrast, the imine **B** which was generated by tautomerization of enamine **A** (path b) would be converted into the intermediate thiiranium ion **C** by an S_N2' type displacement reaction. The ring opening of the thiiranium ion **C** followed by an aromatization reaction of **D** would then provide 6-arylthioindoline **9**. However, the precise reason which dienylimine **8** showed a high level of thiol selectivity in the sequential reaction remains unclear.



Scheme 3. Possible reaction pathway

We next investigated the addition–aromatization reactions of **8** with several alkyl thiols (Scheme 4). The reaction with octanethiol proceeded well to give corresponding indolines **9j** and **10j** in good yields with low regioselectivity, although prolonged warming was required. Furthermore, sequential reaction of **8** with 3-mercaptopropionic acid followed by treatment with trimethylsilyldiazomethane gave corresponding indolines **9k** and **10k** with methoxycarbonyl groups in good yields. Thus, it was clarified that BODIPY fluorophore-containing dienylimine **8** is suitable as a thiol-selective labeling reagent that can recognize a variety of aryl and alkyl thiols.



Scheme 4. Addition–aromatization reactions of dienylimine **8** with alkyl thiols

The fluorescent spectra of compounds **8**, **9a–k**, and **10a–k** are shown in Figure 1. Dienylimine **8** bearing the BODIPY fluorophore was strongly fluorescent. In contrast, the intensity of the fluorescence spectra of indolines **9a–k** and **10a–k**, which were prepared by addition–aromatization reactions of **8** with various aryl and alkyl thiols, was dramatically decreased in all cases. These results suggest that changes in the fluorescence intensity occurred as a consequence of the structural change that occurred on going from the dienylimine moiety to the indoline nucleus.

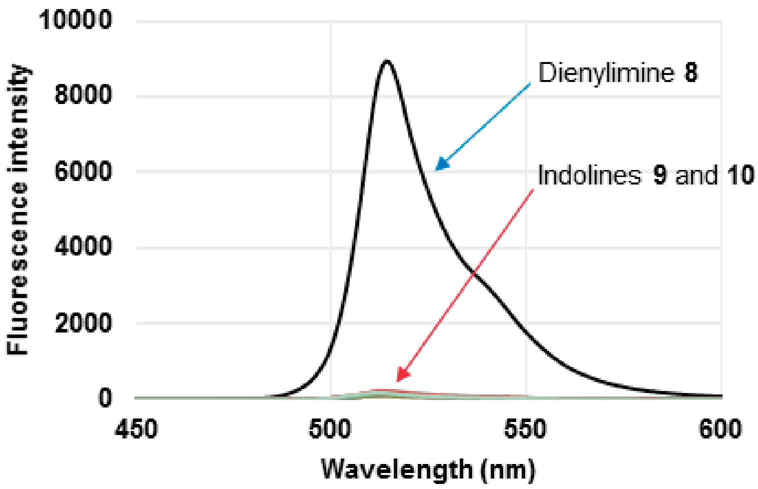


Figure 1. Fluorescence spectra of dienylimine **8** and arylthio and alkylthio indolines **9** and **10**. The spectra were measured at 1.0×10^{-5} M in MeOH. λem (**8**: 514 nm, **9a**: 510 nm, **10a**: 511 nm, **9b**: 514 nm, **10b**: 514 nm, **9c**: 514 nm, **10c**: 514 nm, **9d**: 512 nm, **9e**: 514 nm, **9f**: 514 nm, **9g**: 515 nm, **9h**: 514 nm, **9i**: 514 nm, **9j**: 514 nm, **10j**: 514 nm, **9j**+**10j**: 512 nm).

We would propose fluorescence quenching mechanism by sequential reaction of BODIPY-containing dienylimine **8**, as shown in Figure 2. In our previous report,[9] dienylimine **1** bearing dansyl group as a fluorophore was weakly fluorescent because of donor-excited photoinduced electron transfer (d-PeT) from the fluorophore excited state to the LUMO of the electron-deficient dienylimine moiety. In contrast, BODIPY-containing dienylimine **8** was strongly fluorescent. These results suggested that the LUMO level of the dienylimine moiety would be higher than that of excited BODIPY moiety. In addition, the HOMO level of the dienylimine moiety could be lower than that of BODIPY moiety because both d-PeT

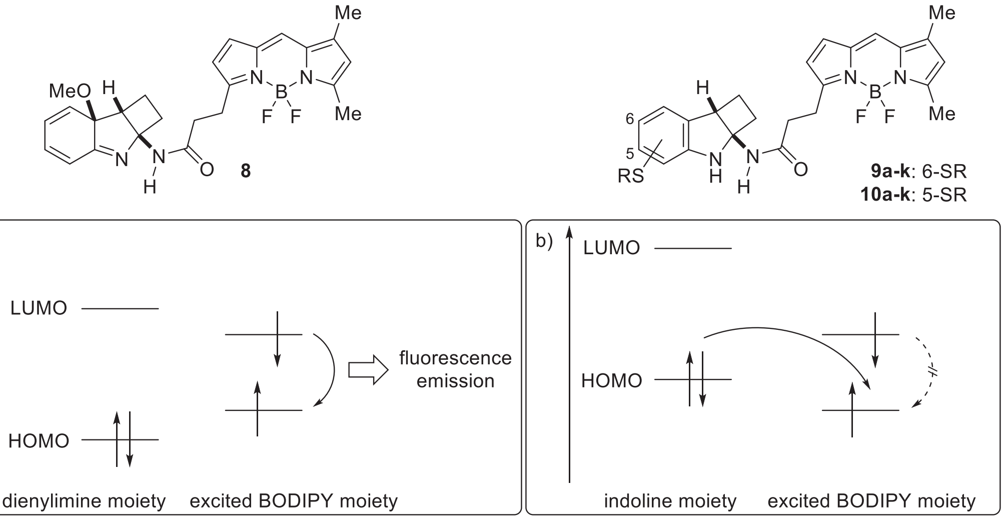


Figure 2. Proposed fluorescence quenching mechanism by photoinduced electron transfer

from BODIPY fluorophore to dienylimine **8** and acceptor-excited photoinduced electron transfer (a-PeT) from **8** to BODIPY fluorophore would not involve. On the other hand, the HOMO level of the indoline moiety (**9** and **10**) could be higher than that of dienylimine. Elevation of the HOMO level by raising the electron density could induce a-PeT process from the HOMO of dienylimine moiety. BODIPY fluorescence was therefore drastically quenched as a consequence of changes in the structure from the electron-deficient dienylimine to the electron-rich indoline.

In summary, we have developed a "turn-off" fluorescent thiol-labeling reagent based on a dienylimine scaffold bearing a BODIPY functionality. Thiol-labeling reagent **8** showed high selectivity toward thiol groups over amino and hydroxyl groups. It is noteworthy that the fluorescence of **8** was quenched as a result of PeT from the electron-rich indoline moiety. We are currently working on modifying the dienylimine core and exploring other fluorophores with the aim of producing a fluorescent "turn-on" labeling reagent for thiols.

EXPERIMENTAL

General information: NMR spectra were recorded at 300 MHz/75 MHz (^{1}H NMR and ^{13}C NMR), 500 MHz/125 MHz (^{1}H NMR and ^{13}C NMR) or 600 MHz/150 MHz (^{1}H NMR and ^{13}C NMR) using Varian Gemini-300 (300 MHz), Varian MERCURY plus 300 (300 MHz), Varian NMR system AS 500 (500 MHz) or Bruker Avance III HD (600 MHz) spectrometers. Chemical shifts (δ) are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constants, and integration. IR spectra were obtained on a Parkin Elmer SpectrumOne A spectrometer. Mass spectra were obtained by ESI method on Thermo Fischer Scientific Exactive. Melting point (uncorrected) was determined on BÜCHI M-565. Flash column chromatography (FCC) was preformed using E. Merck Kieselgel 60 (230-400 mesh). Preparative TLC separations were carried out on precoated silica gel plates (E. Merck 60F$_{254}$). Unless otherwise stated, all the reagents and solvents were used as received from the manufacturer.

3-[4,4-Difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-*s*-indacene-3-yl]-*N*-[(2a*S,7a*S**,7b*R**)-7a-methoxy-1,2,7a,7b-tetrahydro-2a*H*-cyclobuta[*b*]indol-2a-yl]propanamide (8)**

Dienylimine **5**[9] and carboxylic acid **7**[12] bearing BODIPY fluorophore were prepared according to literature procedure. To a solution of dienylimine **5** (1.00 g, 3.49 mmol) in MeOH (70 mL) was added aqueous ammonia solution (28%, 70 mL) was heated at 60 °C for 3.5 h. The MeOH was removed by an evaporator. The resulting aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The formation of amino–dienylimine **6** was confirmed by the ^{1}H NMR spectrum in which the NH signal of the amide group (δ:

7.31 (1H, br s) in **5**) was not observed. The crude product **6** was used to next reaction without further purification. To a solution of carboxylic acid **7**[12] (1.02 g, 3.49 mmol) and amino–dienylimine **6** (663.9 mg, 3.39 mmol) in CH_2Cl_2 (260 mL) were added EDCI (669.0 mg, 3.49 mmol), HOBt (471.6 mg, 3.49 mmol), and *i*Pr_2NEt (1.2 mL, 2.0 mmol) at room temperature. After being stirred at the same temperature for 18 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (*n*-hexane:AcOEt = 2:1) to afford dienylimine **8** carrying BODIPY fluorophore (1.51 g, 93%) as a orange powder. mp >270 °C. IR (neat) 3254, 2929, 1666, 1607 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.07 (s, 1H), 6.87 (d, *J* = 4.0 Hz, 1H), 6.57 (d, *J* = 9.5 Hz, 1H), 6.46 (ddd, *J* = 9.5, 5.0, 1.0 Hz, 1H), 6.39 (ddd, *J* = 9.5, 5.0, 1.0 Hz, 1H), 6.32 (d, *J* = 4.0 Hz, 1H), 6.12-6.08 (m, 3H), 3.35 (dd, *J* = 9.0, 6.5 Hz, 1H), 3.30 (t, *J* = 7.5 Hz, 2H), 3.13 (s, 3H), 2.95-2.89 (m, 1H), 2.63 (t, *J* = 7.5 Hz, 2H), 2.56 (s, 3H), 2.25 (s, 3H), 2.04-1.97 (m, 1H), 1.95-1.90 (m, 1H), 1.22-1.15 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.4, 171.1, 160.1, 157.8, 143.6, 133.7, 133.4, 131.2, 128.9, 128.2, 123.8, 123.7, 120.3, 117.6, 87.7, 86.5, 51.7, 45.9, 36.3, 28.3, 24.6, 14.9, 14.3, 11.3. HRMS (ESI) *m/z*: Calcd for $C_{25}H_{28}O_2N_4BF_2$ (M+H$^+$) 465.2267. Found: 465.2270. NOE was observed between 7b-*H* (δ = 3.35) and C(O)N*H* (δ = 6.12-6.08), 7a-O*CH₃* (δ = 3.13) and C(O)N*H* (δ = 6.12-6.08) in NOESY spectroscopy.

General procedure for addition–aromatization reactions of 8 with various aryl and alkyl thiols.

To a solution of dienylimine **8** (23.2 mg, 0.050 mmol) in THF (0.50 mL) was added aryl or alkyl thiols (0.055 mmol) under an argon atmosphere at room temperature, and the resulting mixture was stirred at 40 °C for several hours. The reaction mixture was then concentrated under reduced pressure. The residue was purified by preparative TLC ($CHCl_3$:MeOH = 20:1 or benzene:AcOEt = 1:2) to give indolines **9** and **10**, as shown in Table 1 and Scheme 4.

3-[4,4-Difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-*s*-indacene-3-yl]-*N*-[(2a*R,7b*S**)-6-(phenylthio)-1,2,3,7b-tetrahydro-2a*H*-cyclobuta[*b*]indol-2a-yl]propanamide (9a)**

Pale orange solid. IR (neat) 3401, 3203, 2944, 1650, 1607 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.22-7.18 (m, 3H), 7.12-7.05 (m, 5H), 6.86 (d, *J* = 4.0 Hz, 1H), 6.54 (br s, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 6.28 (d, *J* = 4.0 Hz, 1H), 6.13 (s, 1H), 5.10 (br s, 1H), 3.65 (dd, *J* = 9.0, 5.5 Hz, 1H), 3.27 (t, *J* = 7.5 Hz, 2H), 2.66-2.48 (m, 7H), 2.44-2.37 (m, 1H), 2.26 (s, 3H), 1.87-1.81 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.7, 160.6, 156.6, 151.5, 144.2, 140.1, 135.2, 135.0, 133.3, 132.7, 130.6, 128.7, 128.1, 127.5, 125.1, 123.8, 120.6, 119.8, 117.4, 109.1, 76.3, 46.9, 36.2, 35.8, 24.63, 24.59, 14.9, 11.3. HRMS (ESI) *m/z*: Calcd for $C_{30}H_{30}ON_4BF_2S$ (M+H$^+$) 543.2196. Found: 543.2200. NOE was observed between 7b-*H* (δ = 3.65) and C(O)N*H* (δ = 6.54) in NOESY spectroscopy.

3-[4,4-Difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-*s*-indacene-3-yl]-*N*-[(2a*R,7b*S**)-5-(phenylthio)-1,2,3,7b-tetrahydro-2a*H*-cyclobuta[*b*]indol-2a-yl]propanamide (10a)**

Pale orange solid. IR (neat) 3401, 3293, 2944, 1654, 1604 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33-7.32 (m, 1H), 7.29-7.26 (m, 3H), 7.22-7.19 (m, 1H), 7.05 (s, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.84 (d, *J* = 4.0 Hz, 1H), 6.69 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.51 (d, *J* = 1.5 Hz, 1H), 6.47 (br s, 1H), 6.27 (d, *J* = 4.0 Hz, 1H), 6.12 (s, 1H), 4.95 (br s, 1H), 3.66 (dd, *J* = 8.5, 5.0 Hz, 1H), 3.25 (t, *J* = 7.5 Hz, 2H), 2.66-2.48 (m, 7H), 2.45-2.39 (m, 1H), 2.26 (s, 3H), 1.86-1.79 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.6, 160.5, 156.7, 151.6, 144.1, 136.5, 135.2, 134.2, 133.3, 131.0, 130.5, 129.0, 128.1, 126.6, 124.4, 123.8, 121.8, 120.5, 117.5, 111.6, 76.4, 46.8, 35.9, 35.8, 24.6, 24.5, 14.9, 11.3. HRMS (ESI) *m/z*: Calcd for $C_{30}H_{30}ON_4BF_2S$ (M+H$^+$) 543.2196. Found: 543.2198. NOE was observed between 7b-*H* (δ = 3.66) and C(O)N*H* (δ = 6.47) in NOESY spectroscopy.

3-[4,4-Difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-*s*-indacene-3-yl]-*N*-[(2a*R,7b*S**)-6-[(4-fluorophenyl)thio]-1,2,3,7b-tetrahydro-2a*H*-cyclobuta[*b*]indol-2a-yl]propanamide (9b)**

Pale orange solid. IR (neat) 3401, 3305, 2949, 1656, 1607 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.17-7.06 (m, 5H), 6.96-6.85 (m, 3H), 6.51 (br s, 1H), 6.50 (d, *J* = 8.0 Hz, 1H), 6.28 (d, *J* = 4.0 Hz, 1H), 6.14 (s, 1H), 5.10 (br s, 1H), 3.68-3.62 (m, 1H), 3.26 (t, *J* = 7.5 Hz, 2H), 2.67-2.34 (m, 8H), 2.26 (s, 3H), 1.88-1.78 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.7, 161.2 (d, *J* = 243 Hz), 160.7, 156.6, 151.4, 144.2, 135.3, 134.74, 134.72, 134.4, 133.3, 132.8, 130.0, 129.6 (d, *J* = 7.5 Hz), 128.1, 123.8, 120.8, 120.6, 115.9 (d, *J* = 21.5 Hz), 109.1, 76.3, 46.9, 36.2, 35.9, 24.7, 24.6, 15.0, 11.4. HRMS (ESI) *m/z*: Calcd for $C_{30}H_{29}ON_4BF_3S$ (M+H$^+$) 561.2102. Found: 561.2103.

3-[4,4-Difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-*s*-indacene-3-yl]-*N*-[(2a*R,7b*S**)-5-[(4-fluorophenyl)thio]-1,2,3,7b-tetrahydro-2a*H*-cyclobuta[*b*]indol-2a-yl]propanamide (10b)**

Pale orange solid. IR (neat) 3401, 3301, 2929, 1652, 1607 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.35 (br dd, *J* = 8.5, 5.5 Hz, 2H), 7.06 (s, 1H), 7.00 (br t, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.85 (d, *J* = 4.0 Hz, 1H), 6.61 (d, *J* = 8.0, 1.5 Hz, 1H), 6.45-6.44 (m, 2H), 6.27 (d, *J* = 4.0 Hz, 1H), 6.13 (s, 1H), 4.87 (br s, 1H), 3.65 (br dd, *J* = 7.0, 4.5 Hz, 1H), 3.25 (t, *J* = 7.5 Hz, 2H), 2.67-2.58 (m, 2H), 2.56-2.47 (m, 5H), 2.44-2.40 (m, 1H), 2.26 (s, 3H), 1.84-1.79 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.7, 162.2 (d, *J* = 245 Hz), 160.5, 156.7, 151.7, 135.2, 135.1, 133.5 (d, *J* = 8.0 Hz), 133.3, 131.1, 130.8, 128.1, 124.4, 123.8, 120.9, 120.6, 117.4, 116.3 (d, *J* = 22 Hz), 115.7, 110.7, 76.4, 46.8, 36.0, 35.9, 24.65, 24.56, 15.0, 11.4. HRMS (ESI) *m/z*: Calcd for $C_{30}H_{29}ON_4BF_3S$ (M+H$^+$) 561.2102. Found: 561.2106.

3-[4,4-Difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-*s*-indacene-3-yl]-*N*-[(2a*R,7b*S**)-6-[(4-methoxyphenyl)thio]-1,2,3,7b-tetrahydro-2a*H*-cyclobuta[*b*]indol-2a-yl]propanamide (9c)**

Pale orange solid. IR (neat) 3400, 3305, 2945, 1653, 1607 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.20 (d, *J* = 8.5 Hz, 2H), 7.10 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.05-7.03 (m, 2H), 6.85 (d, *J* = 4.0 Hz, 1H), 6.80 (d, *J* = 8.5 Hz, 2H), 6.49-6.47 (m, 2H), 6.28 (d, *J* = 4.0 Hz, 1H), 6.13 (s, 1H), 5.01 (br s, 1H), 3.77 (s, 3H), 3.65-3.60

(m, 1H), 3.26 (t, J = 7.5 Hz, 2H), 2.66-2.33 (m, 8H), 2.26 (s, 3H), 1.86-1.77 (m, 1H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 171.7, 160.6, 158.4, 156.7, 150.7, 144.2, 135.3, 133.3, 133.0, 132.6, 131.2, 129.3, 128.8, 128.1, 123.8, 123.0, 120.6, 117.4, 114.6, 109.2, 76.4, 55.4, 47.0, 36.1, 35.9, 24.7, 24.6, 15.0, 11.4. HRMS (ESI) *m/z*: Calcd for $C_{31}H_{32}O_2N_4BF_2S$ (M+H$^+$) 573.2302. Found: 573.2302.

3-[4,4-Difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-*s*-indacene-3-yl]-*N*-[(2a*R,7b*S**)-5-[(4-methoxyphenyl)thio]-1,2,3,7b-tetrahydro-2a*H*-cyclobuta[*b*]indol-2a-yl]propanamide (10c)**

Pale orange solid. IR (neat) 3404, 3253, 2942, 1645, 1606 cm^{-1}. ^{1}H NMR (600 MHz, CDCl$_3$) δ: 7.40 (d, J = 8.5 Hz, 2H), 7.05 (s, 1H), 6.88 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 4.0 Hz, 1H), 6.82 (br d, J = 8.0 Hz, 1H), 6.52 (dd, J = 8.0, 1.0 Hz, 1H), 6.42 (br s, 1H), 6.34 (d, J = 1.0 Hz, 1H), 6.26 (d, J = 4.0 Hz, 1H), 6.12 (s, 1H), 4.72 (br s, 1H), 3.82 (s, 3H), 3.62 (dd, J = 7.5, 4.5 Hz, 1H), 3.25 (t, J = 7.5 Hz, 2H), 2.65-2.59 (m, 2H), 2.56-2.45 (m, 5H), 2.42-2.34 (m, 1H), 2.26 (s, 3H), 1.82-1.77 (m, 1H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 171.6, 160.5, 159.6, 156.8, 151.5, 144.1, 137.4 135.2, 135.0, 133.3, 129.7, 128.2, 125.0, 124.2, 123.8, 120.5, 119.0, 117.5, 114.9, 109.0, 76.4, 55.4, 46.8, 35.90, 35.86, 24.63, 24.56, 15.0, 11.4. HRMS (ESI) *m/z*: Calcd for $C_{31}H_{32}O_2N_4BF_2S$ (M+H$^+$) 573.2302. Found: 573.2304.

3-[4,4-Difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-*s*-indacene-3-yl]-*N*-[(2a*R,7b*S**)-6-[(4-aminophenyl)thio]-1,2,3,7b-tetrahydro-2a*H*-cyclobuta[*b*]indol-2a-yl]propanamide (9d)**

Pale orange solid. IR (neat) 3390, 3003, 2948, 1656, 1606 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.14 (d, J = 8.5 Hz, 2H), 7.06-7.03 (m, 2H), 6.97-6.96 (m, 1H), 6.84 (d, J = 4.0 Hz, 1H), 6.59 (d, J = 8.5 Hz, 2H), 6.51 (br s, 1H), 6.44 (d, J = 8.0 Hz, 1H), 6.26 (d, J = 4.0 Hz, 1H), 6.13 (s, 1H), 3.62-3.57 (m, 1H), 3.25 (t, J = 7.5 Hz, 2H), 2.64-2.32 (m, 8H), 2.26 (s, 3H), 1.86-1.77 (m, 1H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 171.7, 160.5, 156.7, 150.3, 145.5, 144.1, 135.2, 133.9, 133.3, 132.5, 131.7, 128.1, 127.7, 125.6, 124.6, 123.8, 120.6, 117.4, 115.7, 109.2, 76.3, 47.1, 36.0, 35.9, 24.7, 24.5, 15.0, 11.3. HRMS (ESI) *m/z*: Calcd for $C_{30}H_{31}ON_5BF_2S$ (M+H$^+$) 558.2305. Found: 558.2308.

3-[4,4-Difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-*s*-indacene-3-yl]-*N*-[(2a*R,7b*S**)-6-[(4-hydroxyphenyl)thio]-1,2,3,7b-tetrahydro-2a*H*-cyclobuta[*b*]indol-2a-yl]propanamide (9e)**

Pale orange solid. IR (neat) 3396, 3007, 2948, 1656, 1607 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.15 (d, J = 8.5 Hz, 2H), 7.10-7.05 (m, 2H), 7.01-6.99 (m, 1H), 6.84 (d, J = 4.0 Hz, 1H), 6.72 (d, J = 8.5 Hz, 2H), 6.54 (br s, 1H), 6.47 (d, J = 8.0 Hz, 1H), 6.27 (d, J = 4.0 Hz, 1H), 6.14 (s, 1H), 3.66-3.60 (m, 1H), 3.26 (t, J = 7.5 Hz, 2H), 2.66-2.61 (m, 2H), 2.56-2.35 (m, 6H), 2.26 (s, 3H), 1.86-1.75 (m, 1H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 172.0, 160.7, 156.4, 154.8, 150.6, 144.3, 135.3, 133.3, 132.7, 132.6, 131.6, 128.9, 128.5, 128.1, 123.8, 123.4, 120.7, 117.4, 116.1, 109.2, 76.3, 47.0, 36.0, 35.9, 24.7, 24.5, 15.0, 11.4. HRMS (ESI) *m/z*: Calcd for $C_{30}H_{30}O_2N_4BF_2S$ (M+H$^+$) 559.2145. Found: 559.2148.

3-[4,4-Difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-*s*-indacene-3-yl]-*N*-[(2a*R,7b*S**)-6-[(3-amino-**

phenyl)thio]-1,2,3,7b-tetrahydro-2a*H*-cyclobuta[*b*]indol-2a-yl]propanamide (9f)

Pale orange solid. IR (neat) 3390, 3003, 2948, 1656, 1606 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.18 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.10-7.06 (m, 2H), 6.99 (t, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 4.0 Hz, 1H), 6.54-6.50 (m, 3H), 6.42-6.39 (m, 2H), 6.28 (d, *J* = 4.0 Hz, 1H), 6.13 (s, 1H), 3.62-3.57 (m, 1H), 3.25 (t, *J* = 7.5 Hz, 2H), 2.64-2.32 (m, 8H), 2.26 (s, 3H), 1.86-1.77 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.8, 160.6, 156.6, 151.4, 146.8, 144.2, 141.1, 135.3, 135.1, 133.3, 132.6, 130.7, 129.5, 128.1, 123.8, 120.6, 119.9, 117.3, 113.4, 112.2, 109.1, 76.3, 46.9, 36.2, 35.8, 24.7, 24.6, 15.0, 11.4. HRMS (ESI) *m/z*: Calcd for $C_{30}H_{31}ON_5BF_2S$ (M+H$^+$) 558.2305. Found: 558.2300.

3-[4,4-Difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-*s*-indacene-3-yl]-*N*-[(2a*R,7b*S**)-6-[(3-hydroxyphenyl)thio]-1,2,3,7b-tetrahydro-2a*H*-cyclobuta[*b*]indol-2a-yl]propanamide (9g)**

Pale orange solid. IR (neat) 3401, 1648, 1606 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.17 (br d, *J* = 7.5 Hz, 1H), 7.11 (s, 1H), 7.07-7.04 (m, 2H), 6.94-6.85 (m, 2H), 6.84 (d, *J* = 7.5 Hz, 1H), 6.55 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.47 (d, *J* = 8.0 Hz, 1H), 6.38 (s, 1H), 6.22 (d, *J* = 4.0 Hz, 1H), 6.12 (s, 1H), 4.80 (br s, 1H), 3.71 (br dd, *J* = 8.5, 5.5 Hz, 1H), 3.20 (t, *J* = 7.5 Hz, 2H), 2.59-2.34 (m, 8H), 2.24 (s, 3H), 1.84-1.79 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 172.3, 160.6, 156.8, 156.5, 151.7, 144.3, 141.9, 135.4, 135.3, 133.3, 133.2, 130.8, 129.7, 128.2, 123.9, 120.7, 119.2, 118.4, 117.4, 113.1, 112.3, 109.1, 76.3, 46.9, 36.1, 35.7, 24.6, 24.5, 15.0, 11.4. HRMS (ESI) *m/z*: Calcd for $C_{30}H_{30}O_2N_4BF_2S$ (M+H$^+$) 559.2145. Found: 559.2140.

3-[4,4-Difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-*s*-indacene-3-yl]-*N*-[(2a*R,7b*S**)-6-[(2-aminophenyl)thio]-1,2,3,7b-tetrahydro-2a*H*-cyclobuta[*b*]indol-2a-yl]propanamide (9h)**

Pale orange solid. IR (neat) 3405, 2946, 1656, 1606 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.12 (td, *J* = 7.5, 1.5 Hz, 1H), 7.03 (s, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.89 (m, 1H), 6.83 (d, *J* = 4.0 Hz, 1H), 6.72-6.61 (m, 2H), 6.47-6.42 (m, 2H), 6.25 (d, *J* = 4.0 Hz, 1H), 6.12 (s, 1H), 4.86 (br s, 1H), 4.23 (br s, 2H), 3.59 (dd, *J* = 8.5, 5.0 Hz, 1H), 3.24 (t, *J* = 7.5 Hz, 2H), 2.63-2.23 (m, 8H), 2.25 (s, 3H), 1.84-1.73 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.7, 160.5, 156.7, 150.1, 147.4, 144.1, 135.2, 133.3, 132.8, 129.8, 129.6, 128.2, 125.9, 123.8, 123.1, 120.6, 118.6, 117.4, 115.3, 109.3, 76.3, 47.0, 36.0, 35.8, 24.6, 24.5, 15.0, 11.4. HRMS (ESI) *m/z*: Calcd for $C_{30}H_{31}ON_5BF_2S$ (M+H$^+$) 558.2305. Found: 558.2310.

3-[4,4-Difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-*s*-indacene-3-yl]-*N*-[(2a*R,7b*S**)-6-[(2-hydroxyphenyl)thio]-1,2,3,7b-tetrahydro-2a*H*-cyclobuta[*b*]indol-2a-yl]propanamide (9i)**

Pale orange solid. IR (neat) 3402, 2949, 1648, 1606 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.46 (dd, *J* = 7.5 1.5 Hz, 1H), 7.29-7.21 (m, 1H), 7.03 (br s, 1H), 7.00-6.80 (m, 5H), 6.64 (br s, 1H), 6.41 (d, *J* = 8.0 Hz, 1H), 6.25 (d, *J* = 4.0 Hz, 1H), 6.12 (s, 1H), 4.85 (br s, 1H), 3.59 (br dd, *J* = 8.5, 5.5 Hz, 1H), 3.24 (t, *J* = 7.5 Hz, 2H), 2.63-2.30 (m, 8H), 2.25 (s, 3H), 1.83-1.72 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 171.7, 160.6, 156.6, 156.3, 150.6, 144.2, 136.2, 135.5, 133.2, 132.9, 131.0, 130.1, 128.1, 126.1, 123.8, 122.3, 121.3, 120.6, 120.2, 117.4, 115.2, 109.2, 76.3, 47.0, 36.1, 35.8, 24.7, 24.5, 15.0, 11.3. HRMS (ESI) *m/z*: Calcd for $C_{30}H_{30}O_2N_4BF_2S$ ($M+H^+$) 559.2145. Found: 559.2140.

3-[4,4-Difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-*s*-indacene-3-yl]-*N*-[(2a*R,7b*S**)-6-(octylthio)-1,2,3,7b-tetrahydro-2a*H*-cyclobuta[*b*]indol-2a-yl]propanamide (9j)**

Pale orange solid. IR (neat) 3398, 3291, 2926, 2855, 1651, 1606 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.10 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.06-7.05 (m, 2H), 6.85 (d, *J* = 4.0 Hz, 1H), 6.50 (br s, 1H), 6.47 (d, *J* = 8.0 Hz, 1H), 6.28 (d, *J* = 4.0 Hz, 1H), 6.13 (s, 1H), 4.97 (br s, 1H), 3.66 (br dd, *J* = 7.5, 5.0 Hz, 1H), 3.26 (t, *J* = 7.5 Hz, 2H), 2.74 (t, *J* = 7.5 Hz, 2H), 2.66-2.41 (m, 8H), 2.26 (s, 3H), 1.88-1.80 (m, 1H), 1.60-1.50 (m, 2H), 1.36-1.25 (m, 10H), 0.87 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.7, 160.5, 156.8, 150.2, 144.1, 135.2, 133.3, 132.5, 132.3, 128.5, 128.1, 123.81, 123.78, 120.6, 117.4, 109.1, 76.3, 47.1, 36.8, 36.0, 35.9, 31.8, 29.4, 29.19, 29.17, 28.7, 24.7, 24.6, 22.6, 15.0, 14.1, 11.3. HRMS (ESI) *m/z*: Calcd for $C_{32}H_{42}ON_4BF_2S$ ($M+H^+$) 579.3135. Found: 579.3138.

3-[4,4-Difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-*s*-indacene-3-yl]-*N*-[(2a*R,7b*S**)-5-(octylthio)-1,2,3,7b-tetrahydro-2a*H*-cyclobuta[*b*]indol-2a-yl]propanamide (10j)**

Pale orange solid. IR (neat) 3401, 3289, 2927, 1651, 1607 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.06 (s, 1H), 6.87-6.85 (m, 2H), 6.63 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.53 (d, *J* = 1.5 Hz, 1H), 6.47 (br s, 1H), 6.28 (d, *J* = 4.0 Hz, 1H), 6.13 (br s, 1H), 4.92 (br s, 1H), 3.63 (br dd, *J* = 8.0, 4.5 Hz, 1H), 3.26 (t, *J* = 7.5 Hz, 2H), 2.85 (t, *J* = 7.5 Hz, 2H), 2.66-2.40 (m, 8H), 2.26 (s, 3H), 1.86-1.78 (m, 1H), 1.68-1.58 (m, 2H), 1.39-1.26 (m, 10H), 0.88 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.7, 160.5, 156.8, 151.3, 144.1, 136.1, 135.2, 133.4, 129.5, 128.2, 124.1, 123.8, 120.5, 119.5, 117.5, 109.5, 76.4, 46.9, 35.9, 34.0, 31.8, 29.7, 29.3, 29.20, 29.16, 28.9, 24.7, 24.6, 22.7, 15.0, 14.1, 11.4. HRMS (ESI) *m/z*: Calcd for $C_{32}H_{42}ON_4BF_2S$ ($M+H^+$) 579.3135. Found: 579.3142.

Methyl 3-[[(2a*R,7b*S**)-2a-[3-(4,4-Difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-*s*-indacene-3-yl)-propanamido]-2,2a,3,7b-tetrahydro-1*H*-cyclobuta[*b*]indol-6-yl]thio]propanoate (9k) and Methyl 3-[[(2a*R**,7b*S**)-2a-[3-(4,4-Difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-*s*-indacene-3-yl)propanamido]-2,2a,3,7b-tetrahydro-1*H*-cyclobuta[*b*]indol-5-yl]thio]propanoate (10k)**

According to the general procedure for addition–aromatization reactions, 3-mercaptopropionic acid (4.79 μL, 0.055 mmol) was added to a solution of dienylimine **8** (23.2 mg, 0.050 mmol) in THF (0.50 mL) at room temperature, and the resulting mixture was stirred at 40 °C for 42 h. The reaction mixture was then concentrated under reduced pressure. The residue was dissolved in MeOH/toluene (v/v = 1:1, 4 mL), and trimethylsilyldiazomethane (0.60 M in *n*-hexane, 0.20 μL, 0.20 mmol) was then added slowly at room temperature. After being stirred at the same temperature for 24 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by preparative TLC ($CHCl_3$:MeOH = 20:1) to give an inseparable mixture of **9k** and **10k** (20.8 mg, 75%, **9k**:**10k** = 5:1) as pale orange solid. IR (neat) 3304, 2949, 1736, 1656, 1606 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.10 (dd, *J* = 7.5, 1.5 Hz, 5/6H), 7.08-7.06 (m, 12/6H), 6.86-6.85 (m, 6/6H), 6.66 (dd, *J* = 7.5, 1.5 Hz, 1/6H), 6.55 (m, 12/6H), 6.46 (d, *J* = 8.0 Hz, 6/6H), 6.27 (d, *J* = 4.0 Hz, 6/6H), 6.13 (s, 6/6H), 3.68-3.64 (m, 24/6H), 3.26 (t, *J* = 7.5 Hz, 12/6H), 3.10 (t, *J* = 7.5 Hz, 2/6H), 2.97 (t, *J* = 7.5 Hz, 10/6H), 2.66-2.40 (m, 60/6H), 2.26 (s, 18/6H), 1.90-1.77 (m, 6/6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.5, 172.3, 171.7, 160.6, 160.5, 156.7, 151.5, 150.9, 144.2, 144.1, 135.3, 134.0, 133.8, 133.3, 132.4, 130.5, 129.5, 128.1, 124.2, 123.8, 121.7, 120.8, 120.6, 117.4, 110.6, 108.9, 76.38, 76.35, 51.8, 51.7, 47.0, 46.8, 36.1, 36.0, 35.9, 34.5, 34.4, 31.9, 29.7, 29.4, 28.7, 24.7, 24.6, 15.0, 11.4. HRMS (ESI) *m/z*: Calcd for $C_{28}H_{32}O_3N_4BF_2S$ ($M+H^+$) 553.2251. Found: 553.2255.

Fluorescence Spectra Measurement

Dienylimine **8**, indolines **9a**–**k** and **10a**–**k** were dissolved in MeOH at a concentration of 1.0×10^{-5} M, and their fluorescence spectra were measured using an F-7000 spectrofluorimeter (Hitachi) with a 1×1 cm quartz cell. The excitation wavelength were set at λmax for each compounds (**8**: 502 nm, **9a**: 504 nm, **10a**: 503 nm, **9b**: 498 nm, **10b**: 501 nm, **9c**: 500 nm, **10c**: 501 nm, **9d**: 502 nm, **9e**: 500 nm, **9f**: 496 nm, **9g**: 497 nm, **9h**: 495 nm, **9i**: 499 nm, **9j**: 501 nm, **10j**: 502 nm, **9j**+**10j**: 503 nm). The slit widths of the excitation and emission were set at 2.5 nm.

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